

REMARKS

Parent Application No. 09/446,717 was subject to a final office action. These remarks address the rejection in that office action with respect to new claims 32 - 54. Where appropriate, Applicants will note which new claims correspond to the claims pending during the previous final office action. The claims have been amended to refer to promoters that are substantially inactive in undifferentiated stem cells. Support for this amendment is found both inherently in the application and at page 4, last paragraph to page 5, second paragraph, page 6, last paragraph, page 12, first paragraph, and page 13, second paragraph. Applicants specifically withdraw all previous arguments regarding the claims and individual claim terms as new claims are being submitted. Thus, the previous arguments should not be viewed as limiting the claims in any way or imparting any meaning the claim terms in the new claims.

The following rejections in the previous final office action will be addressed in order:

1. Claims 15-18, 20, 22-24, and 26-28 in the parent application (corresponding to new claims 32-35, for example), were rejected as allegedly anticipated under 35 U.S.C. §102(b) by Zernicka-Goetz et al.;
2. Claims 15-30 in the parent application (corresponding to new claims 32-54) were rejected as allegedly obvious under 35 U.S.C. §103 in view of Zernicka-Goetz et al. in view of Ikawa et al., and in further view of Wobus et al., Sartorelli et al., and Chen et al.;
3. Claims 26-28 in the parent application (corresponding to new claims 32 and 34-54, for example), were rejected as being non-enabled under 35 U.S.C. §112, first paragraph; and
4. Claims 15 and 17-30 in the parent application were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

1. The Claims are not Anticipated by Zernicka-Goetz et al.

Claims 15-18, 20, 22-24, and 26-28 in the parent application (corresponding to new claims 32-35, for example), were rejected as allegedly anticipated under 35 U.S.C. §102(b) by Zernicka-Goetz et al. The Federal Circuit has stated the relevant analysis for anticipation as follows:

A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference.”

Verdegaal Bros. V. Union Oil Co. Of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As

presented, the Claims require use of a promoter that is substantially inactive in undifferentiated stem cells. In contrast, Zernicka-Goetz et al. teach the use of the cdc2 promoter, which is active in dividing, undifferentiated stem cells. See, for example, Zernicka-Goetz et al. at page 1135, column 2, which teaches that the CDC2 promoter is active in proliferating, undifferentiated cells, and inactive in ES cells that "exit the cell cycle and differentiate in culture." See Hescheler Declaration, Paragraph 3. The cdc2 promoter labels cells from the outset. Thus, tissue-specific expression is not demonstrated. As a result, the claims are not anticipated by Zernicka-Goetz et al.

2. The Claims are Not Obvious Over the Combined References

Claims 15-30 in the parent application (corresponding to new claims 32-54) were rejected as allegedly obvious under 35 U.S.C. §103 in view of Zernicka-Goetz et al. in view of Ikawa et al., and in further view of Wobus et al., Sartorelli et al., and Chen et al. and Claims 1-30 were rejected over the same references further in view of Maltsev et al. and Rohwedel et al. A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and without more entitles the Applicants to allowance of the claims in issue. See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). In addressing this rejection, Applicants focus on the independent claims since the non-obviousness of independent claims necessarily leads to the non-obviousness of claims dependent thereon.¹ As explained below, the Examiner cannot establish a *prima facie* case of obviousness from the previously cited references because there is no motivation to combine the references and no reasonable expectation of success.

a. No Motivation to Combine the References

The Examiner's rejection rests on a factually unsupported (and unsupportable) conclusory

¹ §MPEP 2143.03.

statement. As the Federal Circuit has stated, “[b]efore the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992) (citing *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988)); see also M.P.E.P. § 2143.01. Instead of relying on objective evidence of record, the Examiner has made the following unsupported motivation statement:

Further, it was routine in the art to analyze promoter activity by the expression of a reporter gene, and the artisan would have been motivated to generate the various transgene constructs. As noted in the previous office action, Zernicka-Goetz et al. does not teach the use of Nkx-2.5, human alpha-actin or MLC-2V promoters or the plasmid pCX-(a-act)GFP-Neo, or to use said ES cells in a toxicological assay. Ikawa et al. teach the pCX-GFP vector construct with the beta-actin and CD4 promoters operably linked to GFP for use as a marker in transgenic studies. Wobus et al. teach the MLC-2v promoter which is expressed cardiomyocytes and can be used in toxicological studies, Sartorelli et al. teach the human cardiac alpha-actin promoter, and Chen et al. teach the Nkx-2.5 promoter which is the murine cardiac-specific homeodomain gene. Each of the promoters in reporter vector constructs were used to study the effects on promoter expression, and in particular, Wobus et al. teach to use their vector construct in ES cells induced to develop into cardiomyocytes to study pharmacological and toxicological effects on cardiomyocytes. Applicants argue that one would not exchange one reporter gene for another, or that a promoter driving one gene may be toxic when expressing another gene are unpersuasive because there is no evidence to suggest or support this assertion. To the contrary, in the analysis of a promoter it was routine to use various reporter genes.

This statement is conclusory because it merely recites the references and says that it is routine to combine particular promoters and reporter genes. The Federal Circuit has expressly forbidden this approach hindsight-based approach.

Specifically, the Federal Circuit held that:

The factual inquiry whether to combine references must be thorough and searching. It must be based on **objective evidence** of record. **This precedent has been reinforced in myriad decisions, and cannot be dispensed with.**

See, *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002); internal citations omitted; emphasis added.

Indeed, the Federal Circuit has made it clear that “[b]road, **conclusory** statements regarding the teachings of multiple references, standing alone, are not ‘evidence.’” *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999)(emphasis added).

Thus, the Examiner's conclusory motivation statement falls well short of the standards established by the Federal Circuit. In particular, the Examiner has provided no rationale as to why a person of ordinary skill in the art would be motivated to the references to provide the particular combination of a promoter that is substantially inactive in an undifferentiated stem cell with a reporter gene encoding a fluorescent protein. Given this fact, it is apparent that the Examiner has applied hindsight reconstruction to reject the claims. This is the situation that the above standards are meant to prevent:

The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. **Instead, the Board merely invoked the high level of skill in the art.** If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness (Emphasis added).

In re Rouffet, 47 USPQ2d 1453 (Fed. Cir. 1998). As in *Rouffet*, the Examiner in the parent case substituted a reliance on the high level of skill in the art (i.e., "it was routine in the art to analyze promoter activity by the expression of a reporter gene, and the artisan would have been motivated to generate the various transgene constructs") for a citation to objective evidence of record. Importantly, the Examiner has failed to provide evidence of a motivation to utilize a reporter gene encoding a fluorescent protein in conjunction with a promoter that is not substantially expressed in an undifferentiated stem cell. Accordingly, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because the Federal Circuit standards for motivation to combine have not been met. As such, the obviousness rejection should be removed.

b. There is No Reasonable Expectation of Success

The cited references do not provide a reasonable expectation of success for obtaining the claimed methods. The Federal Circuit has held that "obvious to experiment" is not the standard for obviousness. *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988). The Dow court made it very clear that one must determine whether "the prior art would have suggested to

one of ordinary skill in the art that this process **should** be carried out and **would** have a reasonable likelihood of success, viewed in light of the prior art." *Id.* at 1531 (Emphasis added).

For the following reasons, Applicants submit that one skilled in the art would not believe that a reasonable expectation of success existed for arriving at the claimed invention.

First, Applicants were the first to show that a fluorescent protein (e.g., GFP) could be expressed in high enough amounts from a development dependent that is not expressed in undifferentiated stem cells to overcome background autofluorescence. As documented Paragraph 5 of the accompanying Declaration by the Inventor, Dr. Jürgen Hescheler, the contemporaneous article Raz et al., *Developmental Biology* 203:290-294 (1998)(attached as Tab A to the Declaration) teaches that the number of GFP molecules needed to overcome background autofluorescence is relatively high because GFP is noncatalytic. It is estimated that approximately 10^5 - 10^6 GFP molecules per cell are required to visualize the protein when it is evenly distributed in the cytosol. This low level of sensitivity is expected to result in a time delay between onset of gene expression and the ability to detect accumulated GFP, especially when weak and tightly regulated promoters are used. (See the paragraph bridging the left and right columns of p. 290 of Raz et al.). Thus, a person of skill in the art would not reasonably expect that simply linking a GFP gene to a development dependent promoter would result in detectable expression. Empirical experimentation was required. Moreover, one of ordinary skill in the art would have had no reasonable expectation of success because prior to the presently claimed invention, it was not clear whether promoter leakiness would cause an unspecific expression pattern or whether time-dependent activation of relevant genes would follow the same pattern in stably transfected ES cells as in untransfected ES cell lines.

Second, the cited references in which GFP is used use ubiquitously expressed promoters. For example, Ikawa et al. utilize the chicken beta-actin promoter and analyze expression from the promoter in transgenic mice, not embryoid bodies. The presently claimed approach is completely different from that of Ikawa et al., which generated green mice under the control of a constitutive promoter. Moreover, the senior author Ikawa et al., Dr. Masaru Okabe, indicated in an e-mail to colleagues of the Inventor that GFP may not be a suitable marker for use in embryonic stem cells (see Paragraph 5 of the Hescheler Declaration).

As can be seen, no reasonable expectation existed that the processes and compositions of the present invention **would** have been successful. Many problems existed that were recognized in the art and would have led one of skill in the art to use established reporter systems such as beta-galactosidase instead of the more experimental and less sensitive GFP.

3. The Claims are Enabled

Claims 26-28 in the parent application (corresponding to new claims 32 and 34-54, for example), were rejected as being non-enabled under 35 U.S.C. §112, first paragraph. In particular, Claims 26-28 were rejected because the specification does not enable a method for using differentiated cells in an embryoid body to generate a transgenic mouse. The claims as presented are believed to avoid this rejection.

The independent claims as presented are not limited to the use of mouse cells. The accompanying Declaration by Dr. Hescheler establishes that at the priority date of the application, stem cells and methods of creating embryoid bodies and animals with stem cells were known. As presented in the Table in paragraph 6 of the Declaration, the invention could be practiced with cells from cattle, pigs, rats, primates, hamsters and mink. Thus, it is submitted that the claims are enabled for their full scope.

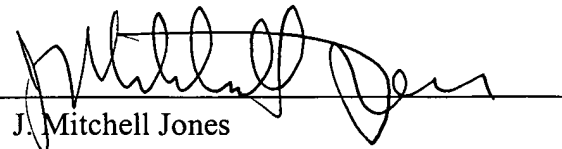
4. The Claims are Definite

Several of the previously pending claims were rejected as indefinite. The Applicants respectfully submit that the newly introduced claims address these issues. Thus, the claims as submitted are definite.

CONCLUSION

All grounds of rejection and objection of the Final Office Action of August 29, 2001 (Paper No. 15 in the parent application) having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: February 4, 2004


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